UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,401	02/19/2004	Philip Ashton-Rickardt	ARCD:390US	4307

32425 7590 10/02/2006

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,401	ASHTON-RICKARDT, PHILIP	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,12-17,21-23,25-31,33,35-37,39-46,49-52,56,59,61,63 and 64* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,12-17,21-23,25-31,33,35-37,39-46,49-52,56,59,61,63 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on July 14, 2006 in response to the Restriction Requirement of 5/17/2006 has been entered. Applicant's election of Group I, claims 1-2, 12-32 and 91, as specifically drawn to a method for modulating cell death in a cell comprising contacting said cell with an SPI2A polypeptide, wherein the cell may be a human patient with an infection has been acknowledged.

Applicants election of Group I with traverse is acknowledged. The traversal is on the grounds that "if the search and examination of an entire application can be made without serious burden, the examiner must examine it one the merits" see MPEP 803. As such, Applicants request inclusion of Groups II-XXXIII and XXXV with Group I because each of the groups is drawn to the amino acid sequence MAGVGCCA or FVVAECCM. Applicants further point out that MAGVGCCA is part of the amino acid sequence of Spi2A, see specification, page 21, lines 23-26, and therefore, searching Spi2A and MAGVGCCA can thus be made without serious burden on the Examiner. Moreover, Applicants point out that a prior art search directed to Spi2A an easily be constructed to include a search of Spi2A polypeptide equivalents. In addition, Applicants assert that each of the diseases set forth in the groups can be easily combined together in a single search string.

These arguments have been carefully considered and have been found persuasive with respect to polypeptides equivalents comprising 4 to 8 consecutive amino acid residues of the amino acid sequence of MAGVGCCA which, in view of the specification is part of the Spi2A and the different diseases. However, these arguments have not been found persuasive with respect to all of the polypeptide equivalents outlined in claim 4 because it is unclear if these equivalents have 4 to 8 consecutive amino acid residues of the amino acid sequence of MAGVGCCA. Moreover, in view of the specification, on page 21, lines 23-26, the amino acids sequence of FVVAECCM appears to be part of SpiB9 and therefore, is not commensurate in scope with the Spi2A amino acid sequence.

As to the question of burden of search for the spi2A equivalents outlined in claim 4, the Examiner recognizes that there are approximately eight different databases that accompany the results of a search of <u>one</u> discrete amino acid or nucleotide sequence and each result set from a particular database must be carefully considered. Hence, the search of

seven different amino acid sequences, and different amino acid segments in the databases would require extensive searching and review. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-6, 12-17, 21-23, 25-31, 33, 35-37, 39-46, 49-52, 56, 59, 61 and 63-64 are currently pending.

Claims 3-5 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-2, 6, 12-17, 21-23, 25-31, 33 35-37, 39-46, 49-52, 56, 59, 61 and 63-64 are currently pending and under consideration.

Note: Due to Applicants arguments being persuasive with respect to the amino acid sequence of MAGVGCCA, claim 6 will be examined to the extent that it reads on a Spi2A polypeptide comprising 4 to 8 consecutive amino acid residues of the amino acid sequence of MAGVGCCA.

Information Disclosure Statement

The Information Disclosure Statements filed on 3/22/2006 and 5/14/2004 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS's are attached hereto.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 1 and 6 are objected to because of the following informalities: In the instant case, claims 1 and 6 recite non elected subject matter in addition to the elected invention of Spi2A.

Claim 6 is further objected for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs:. Hence, the claim 6 fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for

each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 12-17, 21-23, 25-31, 33, 35-37, 39-46, 49-52, 56, 59, 61 and 63-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 12-17, 21-23, 25-31, 33, 35-37, 39-46, 49-52, 56, 59, 61 and 63-64 are rejected as vague and indefinite for reciting the term Spi2A as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify Spi2A, for example, by SEQ ID NO. and function of Spi2A.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 29-31, 33, 35-37, 39-46, 49-52, 56, 59, 61 and 63-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the teachings of the prior art and an in vitro method of modulating cell death in a cell comprising contacting said cell with an Spi2A polypeptide, does not reasonably provide enablement for an in vivo method of modulating cell death in a human comprising contacting said human with an Spi2A polypeptide. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with

additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of modulating cell death in a human subject comprising contacting said human with a Spi2A polypeptide. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of modulating cell death in a human subject comprising contacting said human with a Spi2A polypeptide. The claims are further drawn wherein the patient has an infection, hepatic failure, septic shock, inflammatory disease, a vascular disease, cancer, a bone disease, a viral infection, an autoimmune disorder, multiple sclerosis or arthritis.

Guidance in the specification and Working Examples

The specification teaches that Spi2A inhibits both the caspase pathway and caspase-independent pathway of cell death (page 5, lines 9-10). In particular, the specification (page 60, lines 4-16) teaches that Spi2A inhibited both serine and cysteine proteases, similar to serpin, SQN-5 and also, inhibited the chymotrypsin-like, serine protease cathepsin G, but not elastase or either granzyme B or granzyme A. The specification further provides an example of Spi2A inhibition of caspase-independent cell death (page 61, Example 2). Moreover, the specification contemplates the in vivo prevention of tumor development using Spi2A polypeptides (page 95, Example 6), the treatment of myocardial infarction in

human subjects (page 96, Example 7), the treatment of septic shock in human subjects (Example 8), the treatment of cancer (page 98, Example 9) and the clinical trials using Spi2A polypeptides in the treatment of diseases in general (page 100, example 11). Thus, while the specification provides in vitro testing, as well as contemplates in vivo use, the specification appears to be silent on any correlation between the in vitro testing and in vivo use. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of in vivo use such as for cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that there are eleven human cathepsins which are located within lysosomes, wherein TNF-R1 has been found to trigger cell death independently of caspases by causing lysosomes to release cathepsin B into the cytoplasm. For example, Foghsgaard et al. (J. Cell Biology 2001; 153: 999-1009) teach that cathepsin B inhibitors such as cystatin A and an antisense-mediated depletion of cathepsin B rescued WEHI-S cells from apoptosis triggered by TNF or TNF-related apoptosis-inducing ligand (abstract). Moreover, Foghsgaard et al. teach that cathepsin B acts as an essential downstream mediator of TNF-triggered and caspase-initiated apoptosis cascade. With regards to serpins, those of skill in the art at the time the invention was filed would recognize that the serpin family of protease inhibitors have a well established place in control of extracellular proteolytic cascades, wherein two, human protease inhibitor 6 (PI-6) and PI-9, have recently been found to regulate the intracellular proteases Cathepsin G and granzyme B, as taught by Morris et al. (Biochem. J. 2003; 371: 165-173). Morris et al.

further teach that murin serpin 2A, e.g., Spi2A, has also been found to be localized both in the cytoplasm and the nucleus of the cell and suggest that the biological activities of the protein will be modulated by cellular redox conditions (page 166, 1st column, 1st full paragraph). However, Morris et al. teach that the function of intracellular serpins has largely been inferred from their *in vitro* interaction with target proteases and that there is little evidence to tell us whether their activity is regulated or to explain the significance of the redox-sensitive residues around the reactive site (page 165, 2nd column, paragraph briding 1st column). Thus, while considerable research has gone into to identifying the in vitro function of serpins, one of skill in the art would recognize that a considerable amount of in vitro empirical testing is required, with no *a priori* expectation of success being present, before serpin 2a, e.g., Spi2A can be considered useful for a disease state.

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri

dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 12, 14-15, 17, 21-23, 25-31, 33, 39-40, 49-52, 56, 59, 61 and 63-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillman et al. (US 5,854,023, 1998).

Hillman et al. teach (column 18, lines 3-65 and column 22, lines 13-25) a method of treating infections, neoplastic disorders, an immune disorders in a subject comprising administering an antagonist or a pharmaceutical composition comprising a SHH polypeptide. With regards to the infection, the patent teaches that infections include, but are not limited to, viral infections, hepatitis or smallpox (column 18, lines 3-22). With regards to the neoplastic disorder, the patent teaches that the neoplastic disorders include, but are not limited to, cancer (column 18, lines 26-40). With regards to the immune disorder, the patent teaches that the immune disorders include, but are not limited to, multiple sclerosis, myocardial inflammation, osteoporosis and rheumatoid arthritis (page 18, lines 46-65). With regards to the SAHH polypeptide, the patent teaches that the SAHH polypeptide comprises at least 4 amino acid residues of the instantly claimed amino acid sequence of MAGVGCCA (see below sequence comparison). With regards to the subject, the patent teaches that the subjects include, but are not limited to, humans (column 22, lines 9-12). Thus, while Hillman et al. do not explicitly refer to SAHH as a Spi2A polypeptide, the claimed limitation does not appear to result in a manipulative difference in view of pending claim 6 which recites that a Spi2A polypeptide is a polypeptide comprising 4 to 8 consecutive amino acid residues of the amino acid sequence of MAGVGCCA. As such, the Spi2A polypeptide taught in claim 6 appears to be the same as the prior art. Moreover, while Hillman et al. do not specifically teach that a method for modulating cell death and the further definitions provided in the dependent claims, the Examiner recognizes a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Therefore, because Hillman et al. teaches the active steps of the instant method, the preamble has not been given any patentable weight.

```
MATVTKAPKK QIQFADDMQE FTKFPTKTGR RSLSRSISQS STDSYSSAAS
YTDSSDDEVS PREKQQTNSK GSSNFCVKNI KQAEFGRREI EIAEQDMSAL
ISLRKRAQGE KPLAGAKIVG CTHITAQTAV LIETLCALGA QCRWSACNIY
STQNEVAAAL AEAGVAVFAW KGESEDDFWW CIDRCVNMDG WQANMILDDG
GDLTHWVCKK YPNVFKKIRG IVEESVTGVH RLYQLSKAGK LCVPAMNVND
SVTKQKFDNL YCCRESILDG LKRTTDVMFG GKQVVVCGYG EVGKGCCAAL
                                                ====
KALGAIVYIT EIDPICALQA CMDGFRVVKL NEVIRQVDVV ITCTGNKNVV
TREHLDRMKN SCIVCNMGHS NTEIDVTSLR TPELTWERVR SQVDHVIWPD
GKRVVLLAEG RLLNLSCSTV PTFVLSITAT TQALALIELY NAPEGRYKQD
VYLLPKKMDE YVASLHLPSF DAHLTELTDD QAKYLGLNKN GPFKPNYYRY

HITS represented by underline.
```

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER